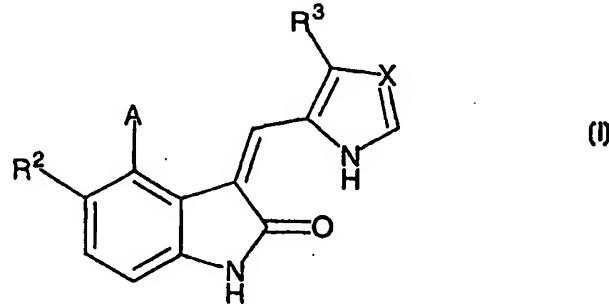




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(71) Applicant:	F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).			
(72) Inventors:	CORBETT, Wendy, Lea; 36 Ridgewood Drive, Randolph, NJ 07869-3754 (US). LUK, Kin-Chun; 66 Evergreen Drive, North Caldwell, NJ 07006-4622 (US). MAHANEY, Paige, E.; 243 Country Club Lane, Scotch Plains, NJ 07076 (US).			
(74) Agent:	LOESCHNER, Thomas; Grenzacherstrasse 124, CH-4070 Basle (CH).			

(54) Title: 4-ARYLOXINDOLES AS INHIBITORS OF JNK PROTEIN KINASES



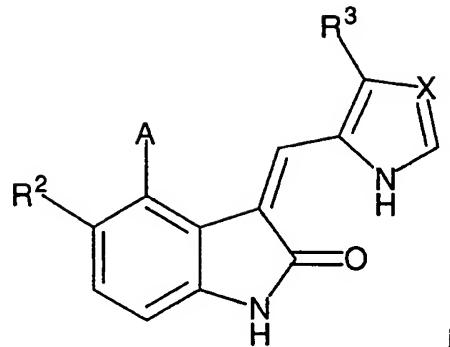
(57) Abstract

Novel 4-aryloxindoles having formula (I), where, R², R³, X and A as set forth in the specification inhibit or modulate protein kinases, in particular JNK protein kinases and are useful as anti-inflammatory agents, particularly in the treatment of rheumatoid arthritis.

CLAIMS

What Is Claimed Is:

5 1. A compound of the formula



and the pharmaceutically acceptable salts of the foregoing compounds,

wherein

- 10 A is aryl or heteroaryl, each of which optionally substituted by one or more -OR⁴, COR⁴, -COOR⁴, -CONR⁶R⁷, -NR⁶R⁷, -CN, -NO₂, -SO₂R⁴, -SO₂NR⁶R⁷, halogen, perfluoroalkyl, lower alkyl, lower alkyl substituted by (a), halogen, cycloalkyl, and/or heterocycle; cycloalkyl or cycloalkyl substituted by (a), halogen, lower alkyl, and/or heterocycle; heterocycle or heterocycle substituted by (a), halogen, lower alkyl, and/or cycloalkyl;
- 15 where (a) is -OR⁴, -NR⁶R⁷, -COR⁴, -COOR⁴, -OCOR⁴, -CONR⁶R⁷, -CN, -NO₂, -SO₂R⁴, or -SO₂NR⁶R⁷;

- 20 R² is hydrogen, -OR⁴, -COOR⁴, -CONR⁶R⁷, -NR⁶R⁷, halogen, -NO₂, -CN, -SO₂NR⁶R⁷, -SO₂R⁴ perfluoroalkyl, lower alkyl, or lower alkyl substituted by -OR⁸, -NR⁶R⁷, -COR⁴, -COOR⁴, and/or -CONR⁶R⁷;

- R³ is hydrogen, -OR⁴, -COR⁴, -COOR⁴, -CONR⁶R⁷, halogen, -CN, -NR⁶R⁷, perfluoroalkyl, lower alkyl, or lower alkyl substituted by -OR⁸ and/or -NR⁶R⁷;

R⁴ is hydrogen, lower alkyl or lower alkyl substituted by (b), cycloalkyl and/or heterocycle; cycloalkyl or cycloalkyl substituted (b), lower alkyl and/or heterocycle; heterocycle or heterocycle substituted by (b), lower alkyl and/or cycloalkyl;

5 where (b) is -OR⁵, -COOR⁸, -COR⁸, -CONR⁸R⁹, -NR⁶R⁷, -CN, -NO₂, -SO₂R⁸, or -SO₂NR⁸R⁹;

R⁵ is hydrogen, -COR⁸, -CONR⁸R⁹, lower alkyl or lower alkyl substituted by -OR⁹, -NR⁹R¹⁰, -N(COR⁹)R¹⁰, -COR⁹, -CONR⁹R¹⁰, and/or -COOR⁹;

10

R⁶ and R⁷ are each independently hydrogen, -COR⁸, -COOR⁸, -CONR⁸R⁹, -SO₂R⁸, -SO₂NR⁸R⁹, lower alkyl or lower alkyl substituted by cycloalkyl (or cycloalkyl substituted by (c), lower alkyl and/or heterocycle), heterocycle (or heterocycle substituted by (c), lower alkyl and/or cycloalkyl), aryl (or aryl substituted by (c), lower

15 alkyl, cycloalkyl and/or heterocycle), or heteroaryl (or heteroaryl substituted by (c), lower alkyl, cycloalkyl and/or heterocycle); or

R⁶ and R⁷ are each independently cycloalkyl or cycloalkyl substituted by (c), lower alkyl and/or heterocycle;

heterocycle (or heterocycle substituted by (c), lower alkyl and/or cycloalkyl),

20 aryl (or aryl substituted by (c), lower alkyl, cycloalkyl and/or heterocycle), or heteroaryl (or heteroaryl substituted by (c), lower alkyl, cycloalkyl and/or heterocycle); where (c) is -OR⁵, -COOR⁸, -COR⁸, -CONR⁸R⁹, -CN, -NO₂, -SO₂R⁸, -SO₂NR⁸R⁹, -NR⁸R⁹;

25 or alternatively, -NR⁶R⁷ forms a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms and being optionally substituted by one or more of lower alkyl, -OR⁵, -COR⁸, -COOR⁸, CONR⁸R⁹, and -NR⁵R⁹;

R⁸ is hydrogen, lower alkyl (or lower alkyl substituted by cycloalkyl, heterocycle, aryl,

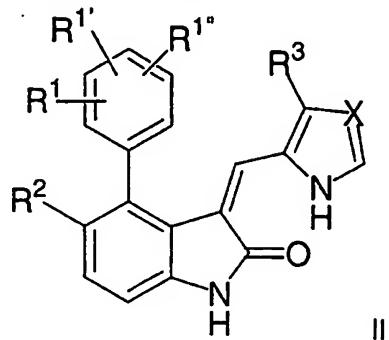
30 heteroaryl, -OR⁹, -NR⁹R¹⁰, and/or -N(COR⁹)R¹⁰),

aryl (or aryl substituted by (d), lower alkyl, cycloalkyl, heterocycle, halogen and /or $-SO_2F$),
heteroaryl (or heteroaryl substituted by (d), lower alkyl, cycloalkyl, heterocycle, halogen and /or $-SO_2F$),
5 cycloalkyl (or cycloalkyl substituted by (d), lower alkyl, heterocycle and/or aryl), or heterocycle (or heterocycle substituted by (d), lower alkyl, cycloalkyl and/or aryl); where (d) is $-OR^9$, $-COOR^9$, $-COR^9$, $-CONR^{10}R^9$, $-NR^{10}R^9$, $-CN$, $-NO_2$, $-SO_2R^9$, or $-SO_2NR^{10}R^9$;
10 R^9 and R^{10} are each independently hydrogen, lower alkyl or aryl; and
X is $=N-$ or $=CH-$.

2. The compounds of claim 1, wherein
15 R^8 is hydrogen, lower alkyl optionally substituted by cycloalkyl, heterocycle, aryl, heteroaryl, $-OR^9$, $-NR^9R^{10}$, and/or $-N(COR^9)R^{10}$; aryl optionally substituted by the group consisting of (d), lower alkyl, cycloalkyl and/or heterocycle; heteroaryl optionally substituted by (d), lower alkyl, cycloalkyl and/or heterocycle;
20 cycloalkyl optionally substituted by (d), lower alkyl, heterocycle and/or aryl; heterocycle optionally substituted by (d), lower alkyl, cycloalkyl and/or aryl; where (d) is $-OR^9$, $-COOR^9$, $-COR^9$, $-CONR^{10}R^9$, $-NR^{10}R^9$, $-CN$, $-NO_2$, $-SO_2R^9$, or $-SO_2NR^{10}R^9$;
 R^9 and R^{10} are each independently hydrogen or lower alkyl;
25 and R^2 , R^3 , A and X are as in claim 1.

3. The compounds of claim 1 or 2 wherein A is aryl or heteroaryl each of which optionally is substituted by $-NR^6R^7$, $-OR^4$, $-COR^4$, $-COOR^4$, $-CONR^6R^7$, $-SO_2R^4$, $-SO_2NR^6R^7$, lower alkyl and/or lower alkyl substituted by $-OR^5$, $-NR^6R^7$, $-COR^4$, $-COOR^4$, and/or $-CONR^6R^7$.

4. The compounds of claim 1 having the formula:



and the pharmaceutically acceptable salts thereof wherein

5 R¹, R^{1'} and R^{1''} are each independently hydrogen, -OR⁴, -COR⁴, -COOR⁴, -CONR⁶R⁷, -NR⁶R⁷, -CN, -NO₂, -SO₂R⁴, -SO₂NR⁶R⁷, halogen, perfluoroalkyl, lower alkyl (or lower alkyl substituted by (a), halogen, cycloalkyl, and/or heterocycle), cycloalkyl (or cycloalkyl substituted by (a), halogen, lower alkyl, and/or heterocycle), heterocycle (or heterocycle substituted by (a), halogen, lower alkyl, and/or cycloalkyl);
10 where (a) is -OR⁴, -NR⁶R⁷, -COR⁴, -COOR⁴, -OCOR⁴, -CONR⁶R⁷, -CN, -NO₂, -SO₂R⁴, or -SO₂NR⁶R⁷;
and R², R³ R⁶, R⁷ and X are as defined in claim 1 for formula I.

5. The compounds of any one of claims 1 to 4 wherein R² is hydrogen, -OB⁴, -

15 NO_2 , $-\text{NR}^6\text{R}^7$, perfluoroalkyl, halogen, $-\text{COR}^4$, $-\text{COOR}^4$, $-\text{CONR}^6\text{R}^7$ lower alkyl and/or lower alkyl substituted by $-\text{OR}^8$ and/or $-\text{NRR}^6\text{R}^7$.

6. The compounds of any one of claims 1 to 5 wherein R³ is hydrogen, -OR⁴ -

NR⁶R⁷, lower alkyl and/or lower alkyl substituted by the group consisting of -OR⁸ and
-NR⁶R⁷.

7. The compounds of any one of claims 1 to 6 wherein R⁴ is selected from the group consisting of -H and lower alkyl which optionally may be substituted by the group consisting of -OR⁵, -COOR⁸, -COR⁸, -NR⁶R⁷ and -CONR⁸R⁹

8. The compounds of any one of claims 1 to 7 wherein R⁵ is selected from the group consisting of -COR⁸, -CONR⁸R⁹, and lower alkyl.

5 9. The compounds of any one of claims 1 to 8 wherein R⁶ and R⁷ are each independently selected from the group consisting of -H, -COR⁸, -COOR⁸, -CONR⁸R⁹, -SO₂R⁸, aryl, heteroaryl and lower alkyl which optionally may be substituted by the group consisting of OR⁵, and -NR⁸R⁹.

10 10. The compounds of any one of claims 1 to 9 wherein R⁸ is selected from the group consisting of -H, aryl, heteroaryl and lower alkyl which optionally may be substituted by the group consisting of aryl, heteroaryl, -OR⁹, -NR⁹R¹⁰, and -N(COR⁹)R¹⁰.

15 11. The compounds of any one of claims 1 to 10 wherein X is =CH-.

12. The compound of claim 1 or 2 wherein A is heteroaryl.

20 13. The compound of claim 12 wherein A is indole or substituted indole.

14. A compound of claim 5 which is

25 (Z)-1,3-Dihydro-4-phenyl-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;
(Z)-4-(3-Aminophenyl)-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-4-(3-Aminophenyl)-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one hydrochloride salt;

30 (Z)-1,3-Dihydro-4-(4-methoxyphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;
(Z)-1,3-Dihydro-4-(3-nitrophenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;
(Z)-1,3-Dihydro-3-[(1H-pyrrol-2-yl)methylene]-4-(3-trifluoromethylphenyl)-2H-indol-2-one;

(Z)-1,3-Dihydro-4-(4-methylphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-1,3-Dihydro-4-(2-methylphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

5 (Z)-4-(2,4-Dichlorophenyl)-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-4-(4-Chlorophenyl)-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-1,3-Dihydro-4-(2-methoxyphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

10 (Z)-1,3-Dihydro-4-(1-naphthalenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-4-(3-Chlorophenyl)-1,3-dihydro-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

15 (Z)-1,3-Dihydro-4-(4-hydroxyphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-4-(3-Aminophenyl)-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-1,3-Dihydro-4-phenyl-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one; or

20 (Z)-1,3-Dihydro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one.

15. A compound of claim 5 which is

25 (Z)-4-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-benzoic acid;

(Z)-3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-benzoic acid;

(Z)-4-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-

30 yl]-benzoic acid;

(Z)-4-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-2-oxo-1H-indol-4-yl]-benzoic acid methyl ester;

(Z)-4-[5-Amino-2,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-4-yl]-benzoic acid methyl ester;

5 (Z)-4-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-5-[(2-thienylacetyl)amino]-1H-indol-4-yl]-benzoic acid methyl ester;

(Z)-4-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-5-[(2-thienylacetyl)amino]-1H-indol-4-yl]-benzoic acid;

10 (Z)-4-[2,3-Dihydro-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2-oxo-1H-indol-4-yl]-benzoic acid methyl ester trifluoroacetate salt;

16. A compound of claim 5 which is

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-4-hydroxybenzamide;

15 (Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methyl]ene]-1H-indol-4-yl]-phenyl]-3-bromobenzamide;

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methyl]ene]-1H-indol-4-yl]-phenyl]-3-cyanobenzamide;

20 (Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-3-nitrobenzamide;

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-4-fluorobenzamide;

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-4-nitrobenzamide;

25 (Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-4-methoxybenzamide;

(Z)-4-Amino-N-[3-[2,3-dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]phenyl]cyclohexanecarboxamide;

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]-phenyl]-4-(fluorosulfonyl)benzamide; or

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(Z)-N-[2-[(3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]phenyl)amino]-2-oxoethyl]-4-(fluorosulfonyl)benzamide;

17. A compound of claim 12 which is
 5 (Z)-1,3-Dihydro-3-[(1H-pyrrol-2-yl)methylene]-4-(2-thiophenyl)-2H-indol-2-one;
 (Z)-1,3-Dihydro-4-(2,4-dimethoxy-6-pyrimidinyl)-3-[(3-methoxy-1H-pyrrol-2-
 yl)methylene]-2H-indol-2-one;
 10 (Z)-1,3-Dihydro-4-(5-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-
 2-one;
 (Z)-1,3-Dihydro-4-(5-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-
 15 2H-indol-2-one,
 (Z)-5-Amino-1,3-dihydro-4-(5-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-
 2H-indol-2-one,
 (Z)-N-[2,3-Dihydro-4-(5-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-
 oxo-1H-indol-5-yl]-2-thiopheneacetamide;
 20 15 (Z)-1,3-Dihydro-4-(4-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-
 2-one;
 (Z)-1,3-Dihydro-4-(6-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-
 2-one;
 25 (Z)-1,3-Dihydro-4-(6-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-
 2H-indol-2-one,
 (Z)-5-Amino-1,3-dihydro-4-(6-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-
 2H-indol-2-one, or
 (Z)-N-[2,3-Dihydro-4-(6-indolyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-
 oxo-1H-indol-5-yl]-2-thiopheneacetamide.

18. A compound of claim 5 which is
 30 (Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-
 yl]phenyl]methanesulfonamide;
 (Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-
 yl]phenyl]-2-thiophenesulfonamide; or

(Z)-N-[3-[2,3-Dihydro-2-oxo-3-[(1H-pyrrol-2-yl)methylene]-1H-indol-4-yl]phenyl]-4-(phenylsulfonyl)-2-thiophenesulfonamide.

19. A compound of claim 5 which is

5 (Z)-1,3-Dihydro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-2H-indol-2-one;

(Z)-1,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-5-nitro-4-phenyl-2H-indol-2-one;

10 (Z)-N-[2,3-Dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-4-phenyl-1H-indol-5-yl]-2-thiopheneacetamide;

(Z)-5-Amino-1,3-dihydro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-N-[2,3-Dihydro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-1H-indol-5-yl]-2-thiopheneacetamide;

15 (Z)-5-Amino-1,3-dihydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-4-phenyl-2H-indol-2-one;

(Z)-1,3-Dihydro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-5-nitro-4-phenyl-2H-indol-2-one; or

20 (Z)-1,3-Dihydro-5-fluoro-4-(4-hydroxyphenyl)-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one trifluoroacetate salt.

20. A compound of claim 1 which is

25 (Z)-1,3-Dihydro-5-fluoro-4-(4-methoxyphenyl)-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one trifluoroacetate salt;

(Z)-1,3-Dihydro-4-(3,4-dimethoxyphenyl)-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one;

(Z)-1,3-Dihydro-4-(2,4-dimethoxyphenyl)-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one;

30 (Z)-4-(1,3-Benzodioxol-5-yl)-1,3-dihydro-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one trifluoroacetate salt;

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(Z)-4-(3-Aminophenyl)-1,3-dihydro-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one;

(Z)-4-(3-Amino-4-methyl-phenyl)-1,3-dihydro-5-fluoro-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one;

5 (Z)-1,3-Dihydro-5-fluoro-4-(3-hydroxyphenyl)-3-[(4-methyl-1H-imidazol-5-yl)methylene]-2H-indol-2-one;

y 10 (Z)-1,3-Dihydro-5-fluoro-4-(4-hydroxyphenyl)-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

(Z)-1,3-Dihydro-5-fluoro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one;

15 (Z)-1,3-Dihydro-5-fluoro-4-(4-hydroxyphenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-2,3-dihydro-1H-2-[3-[5-Fluoro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-oxo-2,3-dihydro-1H-indol-4-yl]-phenylamino]-acetamide; or

(Z)-1,3-Dihydro-5-fluoro-4-(4-hydroxymethyl-3-methoxy-phenyl)-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-indol-2-one.

20 21. (Z)-1,3-Dihydro-4-iodo-3-[(1H-pyrrol-2-yl)methylene]-2H-indol-2-one

22. A pharmaceutical composition comprising as an active ingredient a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

25 23. The compounds of claim 1 for use as medicaments.

24. The use of a compound of claim 1 in the preparation of a medicament containing a compound of claim 1 for treating a neuro-degenerative disease, particularly rheumatoid arthritis.

25. The novel compounds, compositions and use as hereinbefore described, especially with reference to the Examples.

INTERNATIONAL SEARCH REPORT

In National Application No
PCT/EP 99/09673

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/06

A61K31/40

C07D409/14

C07D403/14

C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 40116 A (SUGEN, INC.) 19 December 1996 (1996-12-19) cited in the application page 1 -page 2; claim 1	1,22
A	WO 96 32380 A (PHARMACIA S.P.A.) 17 October 1996 (1996-10-17) cited in the application claims	1,22

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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Authorized officer

Van Bijlen, H

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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